10/511452

Connecting via Winsock to STN

Welcome to STN International! Enter x:x

* * * * * * * * * * STN Columbus * * * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 08:39:33 ON 06 NOV 2006

=> file ca

=> s prodrug? and (simple ester)
15300 PRODRUG?
539852 SIMPLE
580195 ESTER
79 SIMPLE ESTER
(SIMPLE(W)ESTER)
L1 1 PRODRUG? AND (SIMPLE ESTER)

=> d ibib abs

L1 ANSWER 1 OF 1 CA COPYRIGHT 2006 ACS on STN

ACCESSION NUMBER: 132:302814 CA
TITLE: Orally active peptidomimetic RGD analogs that are glycoprotein IIb/IIIa antagonists
AUTHOR(S): Wang, W.; Borchardt, R. T.; Wang, B.
CORPORATE SOURCE: Department of Chemistry, North Carolina State University, Raleigh, NC, 27695, USA
SOURCE: Current Medicinal Chemistry (2000), 7(4), 437-453
CODEN: CMCHE7; ISSN: 0929-8673
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 112 refs. Peptidomimetic RGD (Arg-Gly-Asp) analogs, which bind to glycoprotein (GP) IIb/IIIa on the surface of activated platelets, have been shown to inhibit platelet aggregation. Consequently, such RGD analogs can be used for the treatment of unstable angina pectoris and myocardial infarction. However, the low oral bioavailability for this class of compds. has been hindering their clin. development. Although many factors affect the oral activity of a drug, the limited membrane permeability of RGD analogs due to charge and high polarity is thought to be a major factor leading to the low oral activity of such compds. Another factor is the metabolic lability of some such RGD analogs in the presence of proteases and peptidases. During the last 5 yr, major progress has been made in the development of orally active RGD analogs. To improve the metabolic stability of RGD analogs, N-alkylation and C-terminal modification methods have been used successfully. To improve the membrane permeability of RGD analogs, two major strategies have been used. The first one is the strategy of prodrug. Along this line, simple ester prodrugs, double prodrugs, triple prodrugs, and cyclic prodrugs have been prepared with improved membrane permeability and oral activity. The second approach used is the de novo design of centrally constrained RGD analogs with improved oral bioavailability while maintaining the desired potency against GP IIb/IIIa. The lessons learned from the modification of RGD analogs could also help the future design of other peptidomimetic drugs with improved oral bioavailability.

REFERENCE COUNT: 77 THERE ARE 77 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

```
=> file ca

=> s alkyl ester prodrug?
         571025 ALKYL
         580195 ESTER
          15300 PRODRUG?
L2           23 ALKYL ESTER PRODRUG?
                  (ALKYL(W)ESTER(W)PRODRUG?)

=> s l2 not l1
L3           23 L2 NOT L1

=> d ibib abs 1-23
```

L3 ANSWER 1 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 144:403722 CA
TITLE: In vitro and in vivo evaluation of the metabolism and bioavailability of ester prodrugs of MGS0039 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6- dicarboxylic acid), a potent metabotropic glutamate receptor antagonist
AUTHOR(S): Nakamura, Masato; Kawakita, Yasunori; Yasuhara, Akito; Fukasawa, Yoshiki; Yoshida, Koji; Sakagami, Kazunari; Nakazato, Atsuro
CORPORATE SOURCE: Medical Development Research Laboratories, Taisho Pharmaceutical Co., Ltd., Saitama, Japan
SOURCE: Drug Metabolism and Disposition (2006), 34(3), 369-374
CODEN: DMDSAI; ISSN: 0090-9556
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB MGS0039 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid) has been identified as a potent and selective antagonist for metabotropic glutamate receptors. However, the oral bioavailability of MGS0039 is 10.9% in rats, due to low absorption. Several prodrugs, synthesized to improve absorption, exhibited 40 to 70% bioavailability in rats. This study investigated in vitro metabolism using liver S9 fractions from both cynomolgus monkeys and humans and oral bioavailability in cynomolgus monkeys to select the prodrug most likely to exhibit optimal pharmacokinetic profiles in humans. In monkeys, transformation to active substance was observed (5.9 - 72.8%) in liver S9 fractions, and Bu, n-pentyl, 3-methylbutyl, and 4-methylpentyl ester prodrugs exhibited high transformation ratios (>64%). Cmax levels and F values after oral dosing increased to 4.1- to 6.3-fold and 2.4- to 6.3-fold, resp., and a close relationship between transformation ratios and Cmax and F values was observed, indicating that the hydrolysis rate in liver S9 fractions is the key factor in determining oral bioavailability in monkeys. In humans, n-hexyl, n-heptyl, n-octyl, 5-methylbutyl, and 6-methylpentyl ester prodrugs exhibited high transformation ratios (>65%) in liver S9 fractions. With these prodrugs, n-hexyl, n-heptyl, and 5-methylpentyl ester, almost complete recovery (96 - 99%) was obtained. Given the transformation ratio, we anticipated that the n-heptyl alkyl ester prodrug would exhibit the highest oral bioavailability of active substances in humans, if the hydrolysis rate in liver S9 fractions is indeed the key factor in determining oral bioavailability in humans. On this basis, MGS0210 (3-(3,4-dichlorobenzyloxy)-2-amino-6-fluorobicyclo[3.1.0]hexane-2,6-dicarboxylic acid n-heptyl ester) seems to be a promising candidate among MGS0039 prodrugs.

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:311659 CA
TITLE: Bioconversion of naltrexone and its 3-O-alkyl -ester prodrugs in a human skin equivalent
AUTHOR(S): Hammell, Dana C.; Stolarczyk, Elzbieta I.; Klausner, Mitch; Hamad, Mohamed O.; Crooks, Peter A.; Stinchcomb, Audra L.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY, 40536-0082, USA
SOURCE: Journal of Pharmaceutical Sciences (2005), 94(4), 828-836
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The purpose of this study was to compare the percutaneous absorption and bioconversion of naltrexone (NTX), naltrexone-3-O-valerate (VAL), and naltrexone-3-O-(2'-ethylbutyrate) (ETBUT) in a human skin equivalent model (EpiDerm) and in fresh human skin in vitro. NTX diffusion and metabolism to 6-β-naltrexol (NTXol) were quantitated and compared in the EpiDerm and in excised fresh human skin. VAL and ETBUT diffusion and bioconversion studies were also completed in EpiDerm. Naltrexone bioconverted to levels of 3±2% NTXol in the EpiDerm and 1±0.5% in fresh human skin. VAL hydrolyzed rapidly in the EpiDerm and mainly (93±4%) NTX was found in the receiver compartment, similar to human skin. More intact ETBUT permeated the EpiDerm tissue compared to VAL, and only 15±11% NTX was found in the receiver. Significantly higher fluxes of NTX and the prodrugs were observed with the EpiDerm compared to human skin. A similar flux enhancement level was observed for VAL, compared to NTX base, in the EpiDerm and the human skin. Metabolically active human epidermal models like EpiDerm are useful as an alternative exptl. system to human skin for prediction of topical/transdermal drug/prodrug bioconversion.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 3 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 143:102963 CA
TITLE: In vivo evaluation of 3-O-alkyl ester transdermal prodrugs of naltrexone in hairless guinea pigs
AUTHOR(S): Valiveti, Satyanarayana; Hammell, Dana C.; Paudel, Kalpana S.; Hamad, Mohamed O.; Crooks, Peter A.; Stinchcomb, Audra L.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, University of Kentucky College of Pharmacy, Lexington, KY, 40536-0082, USA
SOURCE: Journal of Controlled Release (2005), 102(2), 509-520
CODEN: JCREEC; ISSN: 0168-3659
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Naltrexone (NTX) is a potent competitive antagonist with high affinity for the μ-opioid receptor. Therapeutically, NTX is used for the treatment of alc. dependence and opioid addiction; however, it does not have the ideal physicochem. properties necessary to achieve therapeutic plasma concns. via the transdermal route. The aim of the present investigation was to evaluate the in vivo transdermal delivery of three 3-O-alkyl ester prodrugs of NTX, including NTX-3-O-acetate (ACE-NTX), NTX-3-O-propionate (PROP-NTX), and NTX-3-O-hexanoate (HEX-NTX) in hairless guinea pigs. The pharmacokinetic parameters for NTX and the 3-O-alkyl ester prodrugs of NTX were determined after i.v. drug administration and topical drug application of transdermal therapeutic systems (TTS) in guinea pigs. The results of the in vivo studies showed mean steady-state plasma concns. of NTX from NTX, ACE-NTX, PROP-NTX and HEX-NTX at 4.2, 25.2, 16.0, and 8.3 ng/mL, resp. These NTX plasma concns. were maintained for 48 h. The results of these in vivo studies demonstrated that ACE-NTX and PROP-NTX prodrugs of NTX were the most promising drug candidates for transdermal delivery.

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 139:386133 CA
TITLE: Synthesis and evaluation of ketorolac ester prodrugs for transdermal delivery
AUTHOR(S): Doh, Hea-Jeong; Cho, Won-Jea; Yong, Chul-Soon; Choi, Han-Gon; Kim, Jung Sun; Lee, Chi-Ho; Kim, Dae-Duk
CORPORATE SOURCE: College of Pharmacy, Pusan National University, Pusan, 609-735, S. Korea
SOURCE: Journal of Pharmaceutical Sciences (2003), 92(5), 1008-1017
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Alkyl esters of ketorolac were synthesized as potential prodrugs for transdermal delivery and evaluated to determine the relationship between their skin permeation characteristics and their physicochem. properties. Solubility of the prodrugs in various vehicles was determined at room temperature while lipophilicity was obtained as 1-octanol/water partition coeffs. (logP) and capacity factors (k') using HPLC. Metabolism of the prodrugs to ketorolac was studied both in rat skin homogenate and in plasma. Rat skin permeation characteristics of the prodrugs saturated in propylene glycol were investigated using the Keshary-Chien permeation system at 37°. An increase in logP and capacity factor values of the prodrugs were observed in proportion to their alkyl chain length. Good linear relationship between the logP values and capacity factor was observed (r2 = 0.92). Prodrugs were rapidly degraded to ketorolac both in the skin homogenate and in plasma following a first-order kinetics. To determine accurate amts. of prodrug permeated, both the prodrug and parent drug concentration in the receptor solution were determined in mole units. The skin permeation rate of the alkyl ester prodrugs was significantly higher with a shorter lag time than that of ketorolac. The permeation rate of ketorolac reached maximum in its 1-Pr ester form as 46.61 nmol/cm2/h, and a parabolic relationship was observed between the permeation rate and the logP values of the prodrugs. Alkyl ester prodrugs of ketorolac having optimum lipophilicity could improve the transdermal delivery of ketorolac.

REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 139:106262 CA
TITLE: Straight-chain naltrexone ester prodrugs: diffusion and concurrent esterase biotransformation in human skin
AUTHOR(S): Stinchcomb, Audra L.; Swaan, Peter W.; Ekabo, Opinya; Harris, Kathleen K.; Browe, Jennifer; Hammell, Dana C.; Cooperman, Todd A.; Pearsall, Michael
CORPORATE SOURCE: Division of Pharmaceutical Sciences, College of Pharmacy, University of Kentucky, Lexington, KY, 40536-0082, USA
SOURCE: Journal of Pharmaceutical Sciences (2002), 91(12), 2571-2578
CODEN: JPMSAE; ISSN: 0022-3549
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Naltrexone (NTX) is an opioid antagonist used for treatment of narcotic dependence and alcoholism. Transdermal naltrexone delivery is desirable to help improve patient compliance. The purpose of this study was to increase the delivery rate of NTX across human skin by using lipophilic alkyl ester prodrugs. Straight-chain naltrexone-3-alkyl ester prodrugs of 2-7 carbons in chain length were synthesized and evaluated. In vitro human skin permeation rates were measured using a flow-through diffusion cell system. The m.ps., solubilities, and skin disposition of the drugs were determined The prodrugs were almost completely hydrolyzed on passing through the skin and appeared as NTX in the receiver compartment. The mean NTX flux from the prodrug-saturated solns. exceeded the flux of NTX base by .apprx.2-7-fold. The amount of drug detected in the skin was significantly greater after treatment with the prodrug solns. compared with treatment with NTX base. The extent of parent drug (NTX) regeneration in the intact skin ranged from 28 to 91%. Higher NTX regeneration percentages in skin appeared to correlate with increased drug delivery rates. Definitively, the highly oil-soluble prodrugs provide a higher NTX flux across human skin in vitro and undergo significant metabolic conversion in the skin.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 6 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 138:343674 CA
TITLE: Rat skin permeation of diclofenac and its prodrugs
AUTHOR(S): Doh, Hea-Jeong; Cho, Won-Jea; Yong, Chul-Soon; Lee, Chi-Ho; Kim, Dae-Duk
CORPORATE SOURCE: College of Pharmacy, Pusan National University, Pusan, 609-735, S. Korea
SOURCE: Yakche Hakhoechi (2001), 31(2), 95-100
CODEN: YAHAEX; ISSN: 0259-2347
PUBLISHER: Korean Society of Pharmaceutics
DOCUMENT TYPE: Journal
LANGUAGE: Korean

AB Various alkyl ester prodrugs of diclofenac were synthesized in order to investigate the relationship between their skin permeation characteristics and physicochem. properties. Solubility in various vehicles was measured at room temperature 1-Octanol/water partition coeffs. (Log P) and capacity factors (k') were measured to determine the lipophilicity of the prodrugs. Stability of prodrugs in the skin extract and homogenate was also investigated before conducting the skin permeation studies. Increases in the Log P and capacity factor values were observed when alkyl esters of diclofenac were prepared Since the aqueous solubility of the prodrugs was not high enough, they were saturated in propylene glycol (PG) for skin permeation studies. Prodrugs were rapidly metabolized to diclofenac, both in skin homogenate and in dermal extract of skin. The skin permeation rate of alkyl ester prodrugs was significantly higher than diclofenac with shorter lag time. Moreover, a parabolic relationship was observed between the permeation rate and the log P values of prodrugs, and the maximum flux was achieved at a log P value of around 4.0.

L3 ANSWER 7 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 136:42724 CA
TITLE: Alkyl ester prodrugs for improved topical delivery of ibuprofen
AUTHOR(S): Bansal, Arvind K.; Khar, R. K.; Dubey, R.; Sharma, A. K.
CORPORATE SOURCE: College of Pharmacy, New Delhi, 110 017, India
SOURCE: Indian Journal of Experimental Biology (2001), 39(3), 280-283
CODEN: IJEBA6; ISSN: 0019-5189
PUBLISHER: National Institute of Science Communication, CSIR
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Topical delivery of ibuprofen directly to the site of inflammation can overcome gastrointestinal side effects associated with its long term oral administration. The set of physicochem. properties necessary for optimum topical delivery of ibuprofen can be imparted by formation of its ester prodrugs. Various alkyl ester prodrugs (Me, Et, Pr, iso-Pr, Bu, iso-Bu, sec-Bu, tert-Bu, n-pentyl, hexyl, heptyl, octyl, lauryl, cetyl and octadecyl esters) were synthesized and studied for their physicochem. properties and activity in the carrageenan induced rat paw edema by topical route. Favorable shift in lipophilicity and self penetration enhancing effect of prodrugs responded in improved topical activity over the parent drug ibuprofen.

REFERENCE COUNT: 14 THERE ARE 14 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 134:21374 CA
TITLE: Enhancement of the systemic and CNS specific delivery of L-dopa by the nasal administration of its water soluble prodrugs
AUTHOR(S): Kao, Huaihung Danny; Traboulsi, Ashraf; Itoh, Soichi; Dittert, Lewis; Hussain, Anwar
CORPORATE SOURCE: Endo Pharmaceuticals, Garden City, NY, 11530, USA
SOURCE: Pharmaceutical Research (2000), 17(8), 978-984
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Kluwer Academic/Plenum Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The present study was conducted to evaluate the utility of the nasal route for the systemic delivery of L-dopa using water soluble prodrugs of L-dopa and to examine if this delivery method will result in preferential delivery to the CNS. Several alkyl ester prodrugs of L-dopa were prepared and their physicochem. properties were determined In vitro hydrolysis rate consts. in buffer, rat plasma, rat brain homogenate, rat CSF, and rat nasal perfusate were determined by HPLC. In vivo nasal expts. were carried out in rats. Levels of L-dopa and dopamine in plasma, CSF, and olfactory bulb were determined using HPLC method with electrochem. detection. All the prodrugs showed improved solubility and lipophilicity with relatively fast in vitro conversion in rat plasma. Absorption was fast following nasal delivery of the prodrugs with bioavailability around 90%. Dopamine plasma levels did not change significantly following nasal administration of the Bu ester prodrug. Olfactory bulb and CSF L-dopa concentration were higher following nasal delivery of the Bu ester prodrug compared to an equivalent i.v. dose. Utilization of water soluble prodrugs of L-dopa via the nasal route in the treatment of Parkinson's disease may have therapeutic advantages such as improved bioavailability, decreased side effects, and potentially enhanced CNS delivery.

REFERENCE COUNT: 29 THERE ARE 29 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 9 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 126:122360 CA
TITLE: Synthesis and evaluation of 5' alkyl ester prodrugs of zidovudine for directed lymphatic delivery
AUTHOR(S): Bibby, David C.; Charman, William N.; A. Charman, Susan; Iskander, Magdy N.; Porter, Christopher J. H.
CORPORATE SOURCE: Department of Pharmaceutics, Victorian College of Pharmacy, Monash University (Parkville Campus), 381 Royal Pde, Parkville, Victoria, 3052, Australia
SOURCE: International Journal of Pharmaceutics (1996), 144(1), 61-70
CODEN: IJPHDE; ISSN: 0378-5173
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The butanoic, lauric, and oleic acid ester prodrugs of the anti-AIDS drug zidovudine (AZT) have been synthesized and assessed for their ability to promote the transport of AZT through the intestinal lymph (a major reservoir for the human immunodeficiency virus (HIV)). The octanol/water partition co-efficient and triglyceride solubility of the AZT prodrugs increased with increasing chain length of the alkyl pro-moiety, and the observed values were consistent with that required for potential intestinal lymphatic transport after oral administration. The intestinal lymphatic transport of AZT and the ester prodrugs was assessed after intraduodenal administration as a micellar lipid solution in an anesthetized rat model. Systemic blood was also sampled in order to estimate the overall extent of absorption.The lymphatic transport of AZT was similar when administered as either AZT alone or the lipophilic ester prodrugs, where the amount of AZT collected in fistulated mesenteric lymph was approx. 0.1-0.2% of the administered dose (15 mg/kg AZT). The extent of absorption of AZT, estimated from the area under the plasma concentration time profiles of AZT, when dosed as either parent compound or the lipophilic esters, was essentially complete. These data suggest that rapid bioconversion of the ester prodrugs to AZT in either the intestinal lumen or the enterocyte limits exploitation of this approach as a means of enhancing the selective lymphatic delivery of AZT.

L3 ANSWER 10 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 125:316126 CA
TITLE: Permeation of buprenorphine and its 3-alkyl-ester prodrugs through human skin
AUTHOR(S): Stinchcomb, Audra L.; Paliwal, Anupam; Dua, Rajesh; Imoto, Hirofumi; Woodard, Ronald W.; Flynn, Gordon L.
CORPORATE SOURCE: College Pharmacy, University Michigan, Ann Arbor, MI, 48109, USA
SOURCE: Pharmaceutical Research (1996), 13(10), 1519-1523
CODEN: PHREEB; ISSN: 0724-8741
PUBLISHER: Plenum
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Homologous 3-alkyl-ester prodrugs (C2 to C4) of buprenorphine with decreased crystallinity have been synthesized and evaluated for transdermal delivery commensurate with opioid dependence treatment. To assess the influence of derivatization on delivery, the permeation of the prodrugs through human skin was determined in vitro. Prodrug metabolism was measured in human blood and skin supernatant in vitro along with chemical hydrolysis controls. The prodrugs' octanol/water partition coeffs. were measured. Without exception, the prodrugs were completely hydrolyzed on passing through the skin and appeared as buprenorphine in the receptor compartment. However, using saturation conditions, in no instance did the buprenorphine flux through skin from a prodrug solution exceed the flux of buprenorphine base itself in vitro. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Moreover, the flux of the acetyl ester, the least hydrophobic of the prodrugs, was not significantly elevated upon stripping the skin. Whether in blood or the skin supernatant, the prodrugs hydrolyzed in an apparent first-order fashion and rate consts. and half-lives were calculated We conclude from the results that the prodrugs' very high octanol/water partition coeffs. (hydrophobicity) placed them in viable tissue layer controlled diffusion. Consequently, one does not derived the potential flux-increasing benefit of reducing crystallinity that was expected.

L3 ANSWER 11 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 124:211800 CA
TITLE: Transdermal prodrug concepts: permeation of buprenorphine and its alkyl esters through hairless mouse skin and influence of vehicles
AUTHOR(S): Imoto, Hirofumi; Zhou, ZiQi; Stinchcomb, Audra L.; Flynn, Gordon L.
CORPORATE SOURCE: Coll. Pharmacy, Univ. Michigan, Ann Arbor, MI, 48109-1065, USA
SOURCE: Biological & Pharmaceutical Bulletin (1996), 19(2), 263-7
CODEN: BPBLEO; ISSN: 0918-6158
PUBLISHER: Pharmaceutical Society of Japan
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In vitro skin permeation of buprenorphine (BUP) and three of its alkyl ester prodrugs was evaluated using hairless mouse skin. The 3 esters selected were the acetyl ester (Ac-BUP), Bu ester (Bu-BUP), and iso-Bu ester (Isb-BUP). These drugs were applied on the skin as saturated slurries in 3 vehicles commonly used to formulate agents for transdermal purposes: propylene glycol, polyethylene glycol 400 (PEG 400), and light mineral oil. Unique solubilities were found for each drug on each vehicle. Fluxes through hairless mouse skin were evaluated for each combination of drug and vehicle using Franz diffusion cells. From PEG 400 formulations, the skin fluxes of BUP, Ac-BUP, Bu-BUP, and Isb-BUP were 0.47, 1.64, 0.33, 0.75 μg/cm2/h, resp. Thus, among the 3 potential prodrugs chosen, only Ac-BUP showed significantly higher skin fluxes than BUP. There were no inter-vehicle differences in the fluxes from saturated slurries between the vehicles. Moreover, all the esters were detected substantially in the form of regenerated parent drug (BUP) in the receptor compartment. Indeed, only Ac-BUP exited the skin in a measurably intact form, but the fraction escaping metabolism in transit was small (approx. 2%). However, based on drug dispositions in the skin, the regeneration of buprenorphine seems to depend on the alkyl chain length of the ester moiety. The molar percentages of regenerated parent drug in whole drug collected from the skin following the permeation expts. were: Ac-BUP, 9.2%; Bu-BUP, 40.7%; Isb-BUP, 9.6%, resp. Thus, only Ac-BUP appears promising as a prodrug of buprenorphine, because it is not overly hydrophilic for skin permeation and is also highly metabolized to the parent compound while in the skin.

L3 ANSWER 12 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 123:350110 CA
TITLE: Transdermal delivery of buprenorphine 3-alkyl -ester prodrugs for treatment of opioid dependence
AUTHOR(S): Stinchcomb, Audra Lynn
CORPORATE SOURCE: Univ. of Michigan, Ann Arbor, MI, USA
SOURCE: (1995) 127 pp. Avail.: Univ. Microfilms Int., Order No. DA9527747
From: Diss. Abstr. Int., B 1995, 56(4), 2034
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable

L3 ANSWER 13 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 121:117540 CA
TITLE: Effect of group substitution on the physicochemical properties of ibuprofen prodrugs
AUTHOR(S): Bansal, Arvind K.; Khar, R. K.; Dubey, R.; Sharma, A. K.
CORPORATE SOURCE: Coll. Pharm., New Delhi, India
SOURCE: Pharmazie (1994), 49(6), 422-4
CODEN: PHARAT; ISSN: 0031-7144
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of alkyl ester prodrugs of ibuprofen was synthesized and studied for its physicochem. properties like aqueous solubility, octanol-water partition coefficient and hydrolysis kinetics in aqueous buffer and human plasma. These physicochem. parameters have a forebearing on the overall activity profile of these prodrugs. Math. relationships have been derived to characterize these properties.

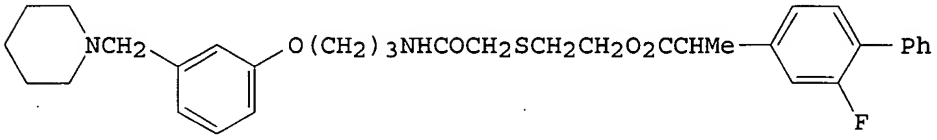
L3 ANSWER 14 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 121:26274 CA
TITLE: Quantitation of activity of alkyl ester prodrugs of ibuprofen
AUTHOR(S): Bansal, A. K.; Dubey, R.; Khar, R. K.
CORPORATE SOURCE: Coll. Pharm., Pushp Vihar, New Delhi, 110 017, India
SOURCE: Drug Development and Industrial Pharmacy (1994), 20(12), 2025-34
CODEN: DDIPD8; ISSN: 0363-9045
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A quant. relationship has been derived for the physicochem. properties and pharmacol. activity of alkyl ester prodrugs of ibuprofen. A comprehensive study consisting of aqueous solubility, octanol-water partition coefficient, hydrolysis kinetics in aqueous buffer (pH 7.4) & human plasma, ulcerogenic studies, anti-inflammatory and analgesic activity was carried on alkyl ester prodrugs of ibuprofen. Pr and Bu esters offered significant improvement in oral delivery of ibuprofen in terms of reduced gastroulcerogenicity and maintenance of pharmacol. activity.

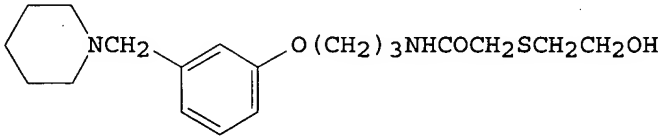
L3 ANSWER 15 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 120:37994 CA
TITLE: Transport and degradation characteristics of methotrexate dialkyl ester prodrugs across tape-stripped hairless mouse skin
AUTHOR(S): Fort, James J.; Shao, Zezhi; Mitra, Ashim K.
CORPORATE SOURCE: Sch. Pharm. Pharmacal Sci., Purdue Univ., West Lafayette, IN, 47907, USA
SOURCE: International Journal of Pharmaceutics (1993), 100(1-3), 233-9
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of methotrexate dialkyl esters were examined with respect to their permeability across tape-stripped hairless mouse skin. The dialkyl esters showed a parabolic permeability vs. side chain length relationship with the di-Me ester being the most permeable compound These compds. were also found to undergo an increased degree of degradation with increased ester chain length during the diffusion process, while with substantially reduced degradation occurring with the branched chain diisopropyl ester. No measurable methotrexate was formed during the course of the experiment, apparently due to the chemical and enzymic stability of the intermediate α- and γ-monoesters.

L3 ANSWER 16 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 115:189560 CA
TITLE: Design and in vivo evaluation of antiinflammatory flurbiprofen chimera drug to reduce gastric irritation
AUTHOR(S): Imai, Teruko; Fukuhara, Akira; Otagiri, Masaki; Ueda, Ikuo
CORPORATE SOURCE: Fac. Pharm. Sci., Kumamoto Univ., Kumamoto, 862, Japan
SOURCE: Drug Delivery System (1991), 6(2), 83-7
CODEN: DDSYEI; ISSN: 0913-5006
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
GI



I



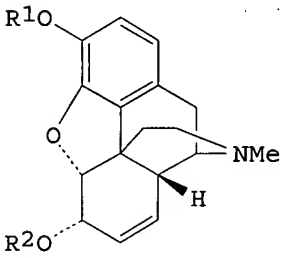
II

AB The anti-inflammatory effect, gastrotoxicity, and in vivo absorption property of a chimera drug (I) of flurbiprofen (FP) with histamine H2-antagonist (II), were compared with those of FP and FP Me ester. I and FP Me ester were only slightly hydrolyzed in a pH 1.2-7.4 buffer in the absence or presence of pepsin and trypsin, in contrast to fast hydrolysis (t1/2 .apprx.20 s) in rat plasma. I inhibited carrageenin-induced paw swelling in the same level as FP alone and reduced gastrotoxicity in comparison to equivalent dose of FP, whereas the coadministration of FP with II did not affect gastrotoxicity of FP. FP Me ester caused slightly less damage to the gastric mucosa than FP alone. The plasma concentration of FP after administration of FP derivs. were similar to FP alone. These data suggested that the chimera drug is effective for reduction of gastric damage, compared with either FP or alkyl ester prodrug like Me ester.

L3 ANSWER 17 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 115:78785 CA
TITLE: Role of enzymic lability in the corneal and conjunctival penetration of timolol ester prodrugs in the pigmented rabbit
AUTHOR(S): Chien, Du Shieng; Sasaki, Hitoshi; Bundgaard, Hans; Buur, Anders; Lee, Vincent H. L.
CORPORATE SOURCE: Sch. Pharm., Univ. South. California, Los Angeles, CA, 90033, USA
SOURCE: Pharmaceutical Research (1991), 8(6), 728-33
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The main objective of this study was to investigate how enzymic lability would affect the extent of corneal and conjunctival penetration of a series of alkyl, cycloalkyl, and aryl ester prodrugs of timolol in the pigmented rabbit. Enzymic lability of the prodrugs was studied in corneal epithelial and conjunctival homogenates, while their corneal and conjunctival penetration was determined using the isolated tissues in the modified Ussing chamber. The straight-chain alkyl and the unsubstituted cycloalkyl esters were hydrolyzed more rapidly than their corresponding branched chain and substituted analogs as well as the aryl esters. The corneal and conjunctival penetration of all prodrugs, regardless of enzymic lability, varied parabolically with lipophilicity. Moreover, the enzymically more labile straight-chain alkyl esters penetrated the cornea and the conjunctiva more readily than the more stable branched-chain esters of comparable lipophilicity. Enzymic lability is, therefore, an addnl. factor that should be considered in designing alkyl ester prodrugs with improved ocular drug delivery characteristics. Enzymic lability does not, however, play as important a role as lipophilicity in the corneal and conjunctival penetration of cycloalkyl and aryl ester prodrugs.

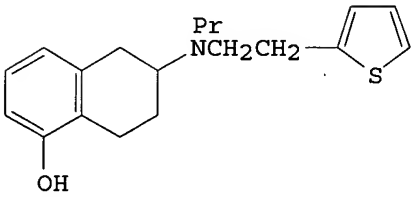
L3 ANSWER 18 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 115:57028 CA
TITLE: Utilization of prodrugs to enhance the transdermal absorption of morphine
AUTHOR(S): Drustrup, Joern; Fullerton, Ann; Christrup, Lona; Bundgaard, Hans
CORPORATE SOURCE: Dep. Pharm. Chem., R. Dan. Sch. Pharm., Copenhagen, DK-2100, Den.
SOURCE: International Journal of Pharmaceutics (1991), 71(1-2), 105-16
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The feasibility of providing transdermal delivery of morphine was examined using the prodrug approach. Various alkyl esters (I, R1 and R2 = COEt, COCHMe2, H, eg.) formed at the 3- and/or 6-hydroxy group in morphine were prepared and their physicochem. and skin penetration properties studied as well as their hydrolysis kinetics. The esters showed generally a higher water and lipid solubility than morphine and were also much more lipophilic than the parent drug in terms of octanol-buffer partition coeffs. Diffusion expts. in vitro using human skin samples showed that whereas morphine did not penetrate the skin to any measurable extent whether applied in the form of saturated solns. in water at pH 7.0 or in iso-Pr myristate, the ester prodrugs showed a high penetrating capacity under the same conditions. Steady-state fluxes up to 35 μg morphine/cm2/h were observed For some esters essentially all of the amts. penetrated were presented in the receptor phase as morphine. The study demonstrates the feasibility of achieving transdermal delivery of morphine based on the ready conversion and the favorable skin penetration properties of morphine esters which in turn are attributed to their combination of adequate water solubility and lipophilicity.

L3 ANSWER 19 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 114:128899 CA
TITLE: Transdermal administration of the dopamine agonist N-0437 and seven ester prodrugs: comparison with oral administration in the 6-OHDA turning model
AUTHOR(S): Den Daas, Izaak; Tepper, Pieter G.; Rollema, Hans; Horn, Alan S.
CORPORATE SOURCE: Univ. Cent. Pharm., State Univ. Groningen, Groningen, NL-9713 AW, Neth.
SOURCE: Naunyn-Schmiedeberg's Archives of Pharmacology (1990), 342(6), 655-9
CODEN: NSAPCC; ISSN: 0028-1298
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB The potent and selective D2-agonist N-0437 (I) undergoes considerable first-pass metabolism after oral administration due to glucuronidation of the phenolic group. In an attempt to improve its bioavailability, seven ester prodrugs of I were synthesized, i.e. the acetyl-, propionyl-, isobutyryl-, pivaloyl-, 2-aminophenyl-, 2-methoxyphenyl- and 2,4-dimethylphenyl-analogs. In vivo activities were assessed by measuring contralateral turning after transdermal administration of I and its prodrugs to rats with unilateral 6-OHDA lesions of the nigrostriatal pathway. From time-effect curves the area under the curve for sep. time intervals was taken as a measure of dopaminergic activity during that interval. Slowly hydrolyzing prodrugs, which are known to show an improved duration of action after oral administration, are devoid of activity after transdermal application. The acetyl-, the propionyl- and the isobutyryl analogs, which are prodrugs with a relatively high hydrolysis rate, were found to have interesting and promising profiles following transdermal application.

L3 ANSWER 20 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 113:158551 CA
TITLE: Prodrug approach of orotic acid using an absorption model
AUTHOR(S): Fuerst, Walter; Neubert, Reinhard; Jurkschat, Thomas; Luecke, Lothar
CORPORATE SOURCE: Sekt. Pharm., Martin-Luther-Univ., Halle-Wittenberg, DDR-4010, Ger. Dem. Rep.
SOURCE: International Journal of Pharmaceutics (1990), 61(1-2), 43-9
CODEN: IJPHDE; ISSN: 0378-5173
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A series of ester prodrugs of orotic acid were synthesized. Using in vitro methods, in particular, an absorption model system, the n-Bu ester of orotic acid was found to be the ester prodrug with optimal physicochem. properties. Pharmacokinetic studies on rabbits confirmed these results. The bioavailability of orotic acid after oral administration of the n-Bu ester prodrug was 3.4-times higher as compared to he methylglucamine salt or orotic acid. A similar increase in bioavailability was predicted based on the in vitro half life for transport in the absorption model.

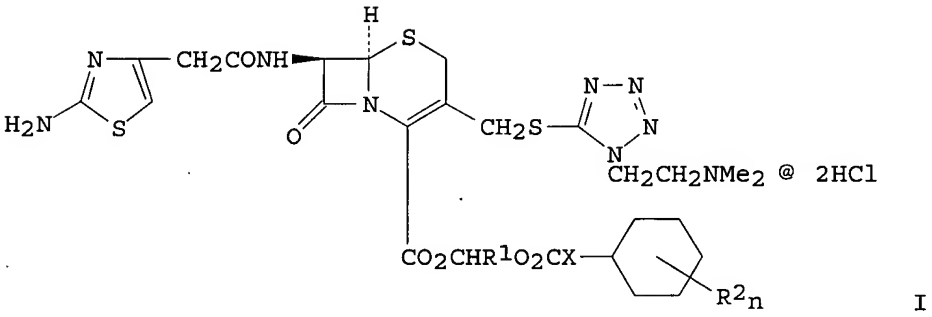
L3 ANSWER 21 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 112:42446 CA
TITLE: Prodrugs of 5-iodo-2'-deoxyuridine for enhanced ocular transport
AUTHOR(S): Narurkar, Milind M.; Mitra, Ashim K.
CORPORATE SOURCE: Sch. Pharm. Pharm. Sci., Purdue Univ., West Lafayette, IN, 47907, USA
SOURCE: Pharmaceutical Research (1989), 6(10), 887-91
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Problems associated with the use of 5-iodo-2'-deoxyuridine (IDU) in the treatment of herpes simplex keratitis can be attributed largely to the polar nature of IDU resulting in its poor permeability across the lipoidal epithelial layer of the corneal membrane. Five aliphatic 5'-esters of IDU were synthesized and evaluated as prodrugs for potential use in the treatment of deep ocular infections such as stromal keratitis, iritis, and even retinitis. A parabolic relationship between in vitro corneal membrane permeability and carbon chain length of prodrugs is evident. For a given prodrug, enzymic hydrolysis proceeded most readily in iris-ciliary body, followed by cornea and aqueous humor. An increase in carbon chain length made the prodrugs more enzymically labile but more resistant to chemical hydrolysis at pH 7.4 and 34°. The 5'-butyryl ester of IDU exhibited an approx. fourfold increase in aqueous humor IDU concentration relative to IDU at 25 min following instillation of 25-μL 5 mM solns.

L3 ANSWER 22 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 111:84015 CA
TITLE: Short-chain alkyl esters of L-dopa as prodrugs for rectal absorption
AUTHOR(S): Fix, Joseph A.; Alexander, Jose; Cortese, Margot; Engle, Karen; Leppert, Paula; Repta, Arnold J.
CORPORATE SOURCE: INTERx Res. Corp., Lawrence, KS, 66046, USA
SOURCE: Pharmaceutical Research (1989), 6(6), 501-5
CODEN: PHREEB; ISSN: 0724-8741
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The bioavailability of L-dopa following rectal administration of a series of short-chain alkyl esters of L-dopa was determined in rats and dogs. The esters were stable (>360 min) to hydrolysis in physiol. buffer. In vitro enzymic hydrolysis of the esters in plasma was species dependent, with the hydrolytic rate being faster in rat plasma (t1/2 < 5 min) than dog plasma (t1/2 = 68-181 min) or human plasma (t1/2 = 96-238 min). In vivo hydrolysis in dogs, as indicated by the L-dopa plasma profile following i.v. administration of the esters, was very rapid (high extravascular esterase activity). Significant L-dopa bioavailability was observed in rats following rectal administration of the Me (46%), Et (14%), iso-Pr (48%), Bu (100%), and 4-hydroxybutyl (13%) esters of L-dopa (rectal L-dopa absorption, <5%). In dogs, significant L-dopa bioavailability was also observed for the Me (28%), iso-Pr (30%), Bu (32%), and 4-hydroxybutyl (34%) esters of L-dopa in the presence of carbidopa. These highly water-soluble (>600 mg/mL) esters of L-dopa are potential candidates for controlled-release rectal delivery systems designed to provide more constant plasma L-dopa levels.

L3 ANSWER 23 OF 23 CA COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 106:188379 CA
TITLE: Orally active 1-(cyclohexyloxycarbonyloxy) alkyl ester prodrugs of cefotiam
AUTHOR(S): Nishimura, Tatsuo; Yoshimura, Yoshinobu; Miyake, Akio; Yamaoka, Masayoshi; Takanohashi, Kunio; Hamaguchi, Naoru; Hirai, Shinichiro; Yashiki, Takatsuka; Numata, Mitsuo
CORPORATE SOURCE: Cent. Res. Div., Takeda Chem. Ind., Ltd., Osaka, 532, Japan
SOURCE: Journal of Antibiotics (1987), 40(1), 81-90
CODEN: JANTAJ; ISSN: 0021-8820
DOCUMENT TYPE: Journal
LANGUAGE: English
GI



I

AB Orally active 1-(alkyl substituted-cyclohexyloxycarbonyloxy)alkyl ester prodrugs (I, R1 = H or alkyl, R2n = H or alkyl, n = 0-2, X = O, S, or NH) of cefotiam (II) [61622-34-2] were studied. The syntheses and oral bioavailability (BA) in mice are described. Among them, I (R1 = Pr, R2n = H, X = O) (III) [95761-79-8] gave the highest BA, 93.5%; the ester having a cyclohexyloxy group in the ester moiety gave BAs of >75%, although the BA of the 1-(ethoxycarbonyloxy)ethyl ester [108098-64-2] was only 23.9%. The thia analog of III [108118-39-4] showed a moderate BA, 46%, but the aza analog of III [108118-37-2], did not show the bioavailability of II. The 1-(substituted cyclohexyloxycarbonyloxy)alkyl group was thus a suitable promoiety to improve the oral BA of II. Chiral 1-(alkoxycarbonyloxy)alkyl groups used as the ester moiety, gave an almost 1:1 mixture of diastereoisomeric esters. These were tested as such. However, an experiment in which the separated isomers of the 1-(cyclohexyloxycarbonyloxy)ethyl ester were administered orally confirmed that both diastereoisomers gave identical BAs.

```
=> d his

     (FILE 'HOME' ENTERED AT 08:39:33 ON 06 NOV 2006)

     FILE 'CA' ENTERED AT 08:40:05 ON 06 NOV 2006
L1             1 S PRODRUG? AND (SIMPLE ESTER)

     FILE 'STNGUIDE' ENTERED AT 08:40:38 ON 06 NOV 2006

     FILE 'CA' ENTERED AT 08:42:06 ON 06 NOV 2006
L2            23 S ALKYL ESTER PRODRUG?
L3            23 S L2 NOT L1

=> s l3 and pain
          42603 PAIN
L4             0 L3 AND PAIN

=
=> d his

     (FILE 'HOME' ENTERED AT 08:39:33 ON 06 NOV 2006)

     FILE 'CA' ENTERED AT 08:40:05 ON 06 NOV 2006
L1             1 S PRODRUG? AND (SIMPLE ESTER)

     FILE 'STNGUIDE' ENTERED AT 08:40:38 ON 06 NOV 2006

     FILE 'CA' ENTERED AT 08:42:06 ON 06 NOV 2006
L2            23 S ALKYL ESTER PRODRUG?
L3            23 S L2 NOT L1
L4             0 S L3 AND PAIN

     FILE 'STNGUIDE' ENTERED AT 08:43:07 ON 06 NOV 2006

=>

---Logging off of STN---


=>
Executing the logoff script...


=> LOG Y

STN INTERNATIONAL LOGOFF AT 08:50:19 ON 06 NOV 2006
```